External beam radiation for the treatment of castration-resistant prostate cancer following primary hormonal therapy with androgen ablation: Analysis and outcome of 21 patients

TEELE KUUSK, KRISTIINA PULLIAINEN and MARKKU H. VAARALA

Division of Operative Care and Medical Research Center Oulu, Oulu University Hospital, 90220 Oulu, Finland

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Abstract. Patients who undergo early androgen-deprivation therapy for prostate cancer may eventually develop castration-resistant prostate cancer. However, no optimal treatment for non-metastasized castration-resistant prostate cancer has yet been established. In the present retrospective, single-institutional study, the radiotherapy (RT) outcomes were evaluated in patients who underwent androgen-deprivation therapy for non-metastatic prostate cancer and subsequently developed castration-resistant disease. Following a thorough chart review, the data of 21 patients with castration-resistant prostate cancer who were treated between 2000 and 2010 with external beam radiation therapy (EBRT) at a prostate radiation dose of >45 Gy were evaluated. Of the 21 patients, 16 (76%) developed biochemical recurrence after RT, with a mean time to biochemical recurrence of 17 months. A total of 18 patients succumbed to the disease during follow-up, with a mean survival of 3 years after RT. A radiation dose of >66 Gy was associated with a longer time to biochemical recurrence after RT (P=0.011) and a longer survival, compared with a dose of ≤66 Gy (P=0.028). The mean overall survival time after RT was 42 months and did not depend on the primary hormonal treatment. Prostate-specific survival time was negatively associated with the Gleason score at diagnosis. The prostate-specific antigen (PSA) concentration prior to RT was a prognostic factor for biochemical recurrence of prostate cancer after RT, as well as for prostate cancer-specific survival. Finally, the multivariate analysis revealed that age, PSA concentration prior to RT and a high Gleason score were independent prognostic factors for prostate cancer-specific survival. Overall, our study findings demonstrated that disease progression was common after EBRT for castration-resistant prostate cancer and that survival was limited. However, young patients and those with low-risk disease at the time of diagnosis may benefit from RT.

Correspondence to: Dr Markku H. Vaarala, Division of Operative Care and Medical Research Center Oulu, Oulu University Hospital, PO Box 21, 90220 Oulu, Finland
E-mail: markku.vaarala@oulu.fi

Abbreviations: CI, confidence interval; CTV, clinical target volume; GnRH, gonadotropin hormone-releasing hormone; GTV, gross tumor volume; HR, hazard ratio; PSA, prostate-specific antigen; PTV, planning target volume

Key words: prostate cancer, radiation, retrospective chart review

Introduction

Prostate cancer is the most common cancer among European men, comprising 12% of all new cancer cases and 5% of all cancer deaths in 2012 (1). There is no evidence that one radical treatment for localized disease is more effective compared with another (2). In a recently published randomized trial, it was demonstrated that radical prostatectomy and radiotherapy (RT) achieved comparable disease control after a 10-year follow-up (3). External beam radiation therapy (EBRT) is a treatment option available at different stages of non-metastatic prostate cancer (4). Androgen-deprivation therapy has also been used as primary treatment for localized prostate cancer (5), leading to apoptotic regression of androgen-dependent tumors. Possible androgen-deprivation therapy regimens include orchiectomy, gonadotropin hormone-releasing hormone (GnRH) agonists, GnRH antagonists and androgen receptor antagonists (6). Use of early androgen-deprivation therapy for prostate cancer may lead to the development of castration-resistant prostate cancer. The median time to bone metastasis in this group of patients is 9-30 months (7,8); the wide time range indicates the heterogeneity of this patient group. Additionally, the treatments and outcomes vary. No consensus on the treatment of non-metastasized castration-resistant prostate cancer has yet been reached. Few published studies have evaluated RT for castration-resistant prostate cancer (9-16). The aim of the present study was to evaluate the outcome of RT among patients who underwent androgen-deprivation therapy as a primary therapy for non-metastatic prostate cancer with progression to castration-resistant disease at our institution between 2000 and 2010.

Patients and methods

Patient chart review. Patient data were obtained through retrospective chart reviews from 2000 to 2010 and based on RT treatment codes. In total, 1,463 patients were treated with EBRT

during this period. Of those, 68 had castration-resistant prostate cancer. Furthermore, 21 of those patients received a prostate radiation dose of >45 Gy. For these patients, RT was administered as salvage treatment for non-metastatic, castration-resistant prostate cancer. Nodal status was systematically assessed only by RT dose planning native computed tomography. Patients with evidently enlarged pelvic lymph nodes were excluded from higher (>45 Gy) prostate radiation doses. Castration-resistant prostate cancer was defined as a progressive increase in the prostate-specific antigen (PSA) concentration in repeated measurements during surgical or chemical (i.e., GnRH agonist therapy) castration. Baseline characteristics, radiation dose, lowest PSA concentration after RT, time to PSA increase (PSA nadir + 2 μg/l) and survival were recorded. The gross tumor volume (GTV) for RT was the prostate gland. The clinical target volume (CTV) was defined as GTV + 1 cm. The seminal vesicles were included in the CTV. The planning target volume (PTV) was defined as the CTV + 1 cm, except for 0.5 cm towards the rectum. If fiducial markers were used in the prostate, the CTV was GTV + 0.5 cm and the PTV was CTV + 0.5 cm, except 0 cm towards the rectum. Only conventional fractionation (2 Gy/fraction) was applied.

Following written assurance that patient information would remain coded and anonymous, this retrospective chart review was exempted from formal Institutional Review Board approval according to Finnish legislation and directions from Finnish ethics committees. The study was conducted according to the principles of the Helsinki Declaration.

Statistical analysis. Data were analyzed using SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA). Between-group comparisons were performed using a t-test. Two-tailed P-values were reported, and P-values <0.05 were considered to indicate statistically significant differences. Prostate cancer-specific survival rates were calculated using the Kaplan-Meier method, and statistical significance between groups was analyzed using the log-rank test. Multivariate prognostic factor analyses were performed using Cox regression analyses.

Results

Patient characteristics. In total, 21 patients with castration-resistant prostate cancer were treated with EBRT with a prostate dose of >45 Gy. The median age of the patients at diagnosis was 68 years (range, 58-75 years). The median age of the patients at the start of EBRT was 74 years (range, 62-80 years). Another concurrent malignancy was present in 3 (14.3%) patients (lung cancer, n=1; malignant melanoma, n=1; and renal cancer, n=1). The Gleason score at diagnosis, clinical T-class [TNM classification (17)], and primary hormonal therapy are presented in Table I. None of the patients had histologically confirmed lymph node metastases at diagnosis. A bone scan was performed to exclude bone metastases at the time of diagnosis in 20 of the 21 patients. The median PSA concentration at the time of diagnosis was 50.2 μg/l (range, 4.8-335.0 μg/l) .

The median time until the PSA nadir was reached was 10 weeks (range, 2-96 weeks). Biochemical progression developed in a median of 41 months (range, 8-110 months). The median lowest PSA concentration was 0.8 μg/l (range, 0.2-25.0 μg/l). All the patients underwent a bone scan prior to RT to exclude metastatic disease; 6 patients (28.6%) also underwent a computed tomography scan and 6 patients (28.6%) underwent abdominal ultrasonography, whereas 1 patient (4.8%) underwent all three diagnostic modalities. The individual patient baseline characteristics are presented in Table II.

Table I. Gleason score and clinical T stage at diagnosis and primary hormonal therapy among the study population (n=21).

TNM classification	N (%)
Gleason score at diagnosis	
≤6	5 (23.8)
7	11 (52.4)
8-10	5 (23.8)
Clinical T stage	
1a-c	3 (14.3)
2a-c	5 (23.8)
3a,b	9 (42.9)
4	4 (19.0)
Primary hormonal therapy	
Antiandrogens	4 (19.0)
Chemical castration	13 (61.9)
Chemical castration + antiandrogen	3 (14.3)
Surgical castration	1 (4.8)

TNM, tumor-node-metastasis.

The median PSA concentration prior to RT was 15.4 μg/l (range, 1.0-219.0 μg/l). The median RT dose was 66 Gy (range, 46-72 Gy) and 10 patients (43.5%) received a dose of 72 Gy. Additionally, 19 patients received pelvic lymph node irradiation, with a median dose of 46 Gy (range, 46-56 Gy).

The mean follow-up duration was 108 months (range, 35-219 months). A total of 18 patients died during the follow-up period: 14 patients (66.7%) succumbed to prostate cancer, whereas 4 (19%) died from other causes, namely chronic obstructive pulmonary disease, intracerebral hemorrhage, gastric cancer and myocardial infarction. Three (14.3%) patients remained alive at the time of the chart review. The individual patient RT dose data and follow-up data are presented in Table III.

The median nadir PSA concentration after RT was 1.8 μg/l (range, 0.1-158 μg/l).

The mean time to the PSA nadir after RT was 5.9 months (range, 1.9-17.0 months). Among patients who developed biochemical recurrence after RT (n=16), the mean time to biochemical recurrence was 17 months [range, 4.7-60.0; 95% confidence interval (CI), 8.4-24.0 months]. Among patients who died during follow-up (n=18), the mean survival after RT was 36 months (range, 3.8-90.0 months).

The radiation dose was associated with the lowest PSA concentration after RT, time to biochemical recurrence after RT, and survival. For patients treated with a prostate radiation dose of ≤66 vs. >66 Gy, the mean lowest PSA concentration after RT was 56.6 and 5.0 μg/l, respectively (P=0.18). The time to biochemical recurrence and survival after RT for patients treated with a prostate radiation dose of ≤66 vs. >66 Gy were

Table II. Baseline characteristics of the patients (n=21).

Patient no.	Age at diagnosis, years	PSA at diagnosis, μg/l	Gleason score	Clinical T stage	Lowest PSA prior to RT, μg/l	PSA prior to RT, μg/l	Time to nadir PSA prior to RT, months	Time to biochemical progression prior to RT, months
1	68	12.0	6	3	0.8	2.1	12	98
2	73	28.6	8	1	2.5	1.0[a]	10	24
3	64	22.4	6	2	0.4	2.4	12	82
4	69	16.2	7	3	1.3	3.0	4	41
5	74	36.7	10	4	1.4	26.7	4	8
6	58	30.7	7	3	0.4	1.5	10	39
7	68	214.0	8	4	5.6	68.2	11	27
8	73	45.1	7	3	0.7	15.4	12	43
9	63	335.0	7	4	25.0	219.0	10	25
10	68	10.8	4	1	0.4	40.1	3	55
11	66	35.4	7	3	0.8	8.6	5	35
12	65	37.7	7	4	0.4	16.1	2	55
13	75	21.1	7	3	3.2	32.7	3	39
14	70	53.3	6	2	12.3	106.8	96	110
15	72	10.3	7	3	3.9	5.9	19	34
16	70	42.3	7	2	0.4	27.4	31	52
17	62	97.6	8	3	0.4	59.6	5	25
18	70	35.8	7	3	0.2	9.7	28	49
19	73	39.9	9	2	3.6	10.0	8	11
20	62	4.8	6	1	1.2	14.4	13	48
21	65	11.6	7	2	0.2	130.0	37	84

[a]The patient had castration-resistant prostate cancer, as determined by an increasing PSA concentration, but maximal androgen blockade was initiated prior to RT. This PSA concentration was the actuarial last measurement prior to RT. RT, radiotherapy; PSA, prostate-specific antigen.

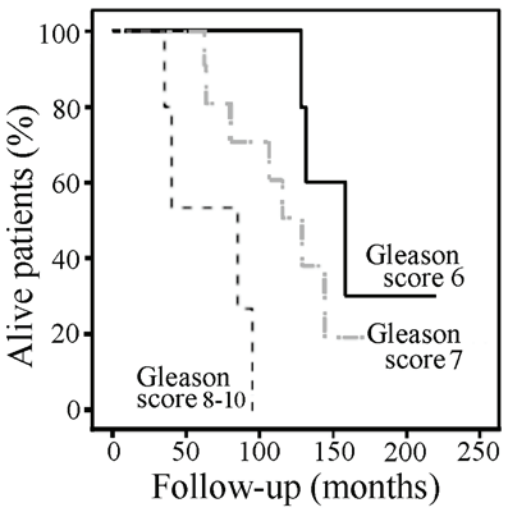

Figure 1. Prostate cancer-specific survival of patients with varying Gleason scores at diagnosis. Survival was significantly lower among patients with high Gleason scores (P=0.002).

8.3 vs. 27 months (P=0.011) and 26 vs. 54 months (P=0.028), respectively.

After RT, the mean overall survival was 42 months (95% CI: 29-55 months). The overall survival did not depend on the primary hormonal treatment. There were no significant differences between different hormonal treatments (data not shown).

The mean prostate-specific survival was negatively associated with the Gleason score at diagnosis (Fig. 1). The mean (95% CI) survival among patients with a Gleason score of ≤6, 7 and ≥8 was 165 (130-201), 119 (95-144), and 66 (36-95) months, respectively (P=0.002).

The PSA level prior to RT was a prognostic factor for biochemical recurrence of prostate cancer after RT [hazard ratio (HR)=1.02; 95% CI: 1.01-1.04; P=0.002). Furthermore, it was a prognostic factor for prostate cancer-specific survival (HR=1.01; 95% CI: 1.00-1.02; P=0.03).

A multivariate analysis was performed, including age, PSA concentration prior to RT and the Gleason score groups. Age, PSA concentration prior to RT and a high Gleason score were independent prognostic factors for prostate cancer-specific survival (Table IV).

Discussion

Castration-resistant prostate cancer without metastases represents a challenge for physicians. Medical or surgical castration

Table III. Radiation therapy dose data and follow-up data of the patients (n=21).

Patient no.	Prostate radiation dose, Gy	Pelvic lymph node radiation dose, Gy	Lowest PSA after RT, μg/l	Time to PSA nadir after RT, months	Time to biochemical recurrence after RT, months	Cause of death	Survival after RT, months	Overall survival/ follow-up months
1	72	46	0.8	6.0	12.4	Prostate cancer	47.8	158
2	66	56	0.1	4.8		Other disease[a]	9.5	36
3	72	50	0.1	7.9		Alive		154
4	72	46	0.4	4.7	59.9	Alive		174
5	66	46	1.9	3.0	9.9	Prostate cancer	30.5	40
6	72	46	0.2	5.6		Alive		131
7	50	50	72.9	5.4	7.3	Prostate cancer	45.2	95
8	72	46				Other disease[b]	3.8	62
9	66	46	105.0	4.6	9.0	Prostate cancer	19.4	62
10	72	56	38.7	1.9	4.9	Prostate cancer	38.6	131
11	72	46	0.4	9.7	35.0	Prostate cancer	86.8	115
12	50	50	86.2	4.0	4.7	Prostate cancer	6.1	64
13	50		65.4	7.7	9.6	Prostate cancer	21.9	81
14	50	50	126.9	3.5	6.6	Prostate cancer	16.1	128
15	50		1.6	3.7	7.9	Prostate cancer	59.2	106
16	50	50	0.9	17.0		Other disease[c]	27.8	120
17	72	46	3.4	4.0	9.5	Prostate cancer	57.8	85
18	72	46	0.2	8.8	33.4	Prostate cancer	89.6	145
19	50	50	3.0	7.3	10.5	Prostate cancer	20.3	35
20	72	46	0.4	5.7	35.8	Other disease[d]	218.8	219
21	46	46	158.7	4.1	9.3	Prostate cancer	32.9	129

[a]Chronic obstructive pulmonary disease. [b]Intracerebral hemorrhage. [c]Gastric cancer. [d]Myocardial infarction.PSA, prostate-specific antigen; RT, radiotherapy.

Table IV. Cox proportional multivariate analysis of patient age at diagnosis, PSA concentration prior to RT and Gleason score at diagnosis as risk factors for prostate cancer death.

Variables	HR	95% CI	P-value
Age at diagnosis	1.25	1.01-1.54	0.04
PSA value prior to RT	1.02	1.00-1.03	0.02
Gleason score			
≤6	1 (ref.)		
7	1.94	0.49-7.74	0.35
≥8	15.9	2.38-106	0.004

PSA, prostate-specific antigen; RT, radiotherapy; HR, hazard ratio; CI, confidence interval.

has been historically used to treat prostate cancer in patients unfit for radical prostatectomy. Castration is currently not recommended for asymptomatic patients with non-metastatic prostate cancer (18). Furthermore, castration may increase the risk of cardiovascular side effects (19). Thus, there must be clear indications, such as severe obstructive voiding symptoms in a patient unsuitable for transurethral resection of the prostate, for castration to be applied; however, some patients are still primarily treated with castration, and this may lead to the need for radical EBRT when primary hormonal therapy fails.

Previous studies have reported the outcome of RT in patients with non-metastatic castration-resistant prostate cancer: To the best of our knowledge, the earliest patient series with a number of patients sufficient for statistical analyses was performed by Lankford *et al* (9), reporting the outcomes of 29 patients: At 4 years, 80% exhibited disease progression or an increasing PSA concentration (9). Botticella *et al* (20) reported that, during a 5-year follow-up, 60% of the 42 patients benefited from EBRT. This was the case for patients with a lower Gleason score, lower T stage and low PSA concentration prior to RT. Moreover, at a median follow-up of 53 months after EBRT, 21 of 42 (50%) patients developed biochemical failure, defined as the nadir PSA + 2 μg/l (20). Among Japanese patients, 66 of 140 (47%) exhibited clinical progression after EBRT during a median follow-up of 20.7 months (12). Another Japanese study presented results from 84 patients with a 3-year progression-free survival (PFS) rate of 61% (21). In an earlier Japanese report containing data from 61 patients (14), the 5-year PFS rate was 43.5%. Another study from Japan (11) presented results from 53 patients: The 3-year clinical relapse-

free survival rate was 78%, and 15 patients developed clinical metastases during a median follow-up of 35 months (11). An Italian study published at the same time reported the data from 29 patients, 24 (83%) of whom had developed biochemical failure after a median of 9.2 months from EBRT (13). A study from Australia reported an actuarial median locoregional PFS duration of 43 months in 34 patients (15); in that study, however, 14 of the 34 patients had metastatic disease at baseline, and the outcome of patients with non-metastatic disease was not specified (15).

In our cohort, 16 of 21 (76%) patients developed biochemical recurrence after RT with a mean time to biochemical recurrence of 17 months. Among patients who died during follow-up (n=18), the mean survival following RT was 3 years.

Our study included a limited population and was retrospective in nature. Possible toxicities were not recorded. The outcomes in our institutional cohort are comparable with those published earlier. However, the benefit of EBRT for castration-refractory prostate cancer appears to be limited, and similar survival may be reached in this population with the novel hormonal treatments abiraterone and enzalutamide. Currently, the use of castration is limited among patients without metastasis, and the need for EBRT with curative intent may be on the decrease.

In conclusion, disease progression following EBRT for castration-resistant prostate cancer was common and survival was limited in the present study. However, certain patients, more likely those who are younger and have low-risk disease at diagnosis, may benefit significantly from RT.

References

1. Prostate (PRC) cancer factsheet. http://www.encr.eu/images/docs/factsheets/ENCR_Factsheet_Prostate_2014.pdf. Accessed September 28, 2016.
2. Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC and Kane RL: Systematic review: Comparative effectiveness and harms of treatments for clinically localized prostate cancer. Ann Intern Med 148: 435-448, 2008.
3. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, Davis M, Peters TJ, Turner EL, Martin RM, *et al*: Study Group: 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med; Epub ahead of print. https://doi.org/10.1056/NEJMoa1606220.
4. Guideline for the management of clinically localized prostate cancer (2007). https://www.auanet.org/education/guidelines/prostate-cancer.cfm. Accessed September 28, 2016.
5. Kawakami J, Cowan JE, Elkin EP, Latini DM, DuChane J and Carroll PR; CaPSURE Investigators: Androgen-deprivation therapy as primary treatment for localized prostate cancer: Data from Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE). Cancer 106: 1708-1714, 2006.
6. Tammela T: Endocrine treatment of prostate cancer. J Steroid Biochem Mol Biol 92: 287-295, 2004.
7. Smith MR, Kabbinavar F, Saad F, Hussain A, Gittelman MC, Bilhartz DL, Wynne C, Murray R, Zinner NR, Schulman C, *et al*: Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol 23: 2918-2925, 2005.
8. Dotan ZA, Bianco FJ Jr, Rabbani F, Eastham JA, Fearn P, Scher HI, Kelly KW, Chen HN, Schöder H, Hricak H, *et al*: Pattern of prostate-specific antigen (PSA) failure dictates the probability of a positive bone scan in patients with an increasing PSA after radical prostatectomy. J Clin Oncol 23: 1962-1968, 2005.
9. Lankford SP, Pollack A and Zagars GK: Radiotherapy for regionally localized hormone refractory prostate cancer. Int J Radiat Oncol Biol Phys 33: 907-912, 1995.
10. Furuya Y, Akakura K, Akimoto S, Ichikawa T and Ito H: Radiotherapy for local progression in patients with hormone-refractory prostate cancer. Int J Urol 6: 187-191, 1999.
11. Akimoto T, Kitamoto Y, Saito J, Harashima K, Nakano T, Ito K, Yamamoto T, Kurokawa K, Yamanaka H, Takahashi M, *et al*: External beam radiotherapy for clinically node-negative, localized hormone-refractory prostate cancer: Impact of pretreatment PSA value on radiotherapeutic outcomes. Int J Radiat Oncol Biol Phys 59: 372-379, 2004.
12. Sasaki T, Nakamura K, Ogawa K, Onishi H, Okamoto A, Koizumi M, Shioyama Y, Mitsumori M and Teshima T; Japanese Patterns of Care Study Working Subgroup on Prostate Cancer: Radiotherapy for patients with localized hormone-refractory prostate cancer: Results of the Patterns of Care Study in Japan. BJU Int 104: 1462-1466, 2009.
13. Sanguineti G, Marcenaro M, Franzone P, Tognoni P, Barra S and Vitale V: Is there a "curative" role of radiotherapy for clinically localized hormone refractory prostate cancer? Am J Clin Oncol 27: 264-268, 2004.
14. Nakamura K, Teshima T, Takahashi Y, Imai A, Koizumi M, Mitsuhashi N, Shioyama Y and Inoue T; Japanese PCS Working Subgroup of Prostate Cancer: Radiotherapy for localized hormone-refractory prostate cancer in Japan. Anticancer Res 24: 3141-3145, 2004.
15. Gogna NK, Baxi S, Hickey B, Baumann K, Burmeister E and Holt T: Split-course, high-dose palliative pelvic radiotherapy for locally progressive hormone-refractory prostate cancer. Int J Radiat Oncol Biol Phys 83: e205-e211, 2012.
16. White R, Khor R, Bressel M, Duchesne G, Williams S, Bowden P, Tai K and Foroudi F: Efficacy of high-dose palliative radiotherapy for localised, castration-resistant prostate cancer. Clin Oncol (R Coll Radiol) 27: 16-21, 2015.
17. Sobin L and Wittekind C: Union for international cancer control: TNM classification of malignant tumours. 6th edition. Wiley, New York, 2002.
18. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, *et al*; European Association of Urology: EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 65: 467-479, 2014.
19. Bosco C, Bosnyak Z, Malmberg A, Adolfsson J, Keating NL and Van Hemelrijck M: Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: A meta-analysis. Eur Urol 68: 386-396, 2015.
20. Botticella A, Guarneri A, Filippi AR, Levra NG, Munoz F, Ragona R, Gontero P and Ricardi U: May non-metastatic clinically localized castration-resistant prostate cancer after primary androgen ablation benefit from salvage prostate radiotherapy? J Cancer Res Clin Oncol 139: 1955-1960, 2013.
21. Ogawa K, Nakamura K, Sasaki T, Onishi H, Koizumi M, Shioyama Y, Araya M, Mukumoto N, Mitsumori M and Teshima T; Japanese Patterns of Care Study Working Subgroup of Prostate Cancer: External beam radiotherapy for clinically localized hormone-refractory prostate cancer: Clinical significance of Nadir prostate-specific antigen value within 12 months. Int J Radiat Oncol Biol Phys 74: 759-765, 2009.